TOPIC HIGHLIGHT

Clinical features and management of primary sclerosing cholangitis

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Received: September 10, 2007   Revised: October 23, 2007
Accepted: October 30, 2007
Published online: June 7, 2008

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Abstract

Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts, resulting in cirrhosis and need for liver transplantation and reduced life expectancy. The majority of cases occur in young and middle-aged men, often in association with inflammatory bowel disease. The etiology of primary sclerosing cholangitis includes immune-mediated components and elements of undefined nature. No effective medical therapy has been identified. The multiple complications of primary sclerosing cholangitis include metabolic bone disease, dominant strictures, bacterial cholangitis, and malignancy, particularly cholangiocarcinoma, which is the most lethal complication of primary sclerosing cholangitis. Liver transplantation is currently the only life-extending therapeutic alternative for patients with end-stage disease, although recurrence in the allografted liver has been described. A PSC-like variant attracting attention is cholangitis marked by raised levels of the immunoglobulin G4 subclass, prominence of plasma cells within the lesions, and steroid responsiveness.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammatory destruction of the intrahepatic and/or extrahepatic bile ducts[1], leading to bile stasis, hepatic fibrosis, and ultimately to cirrhosis, end-stage liver disease, and need for liver transplantation. The majority of cases occur in association with inflammatory bowel disease (IBD), which often precedes the development of PSC[2]. The etiology of PSC is undefined, apart from an increasing body of evidence that points to an immunologic disturbance as a component of the disease. However, PSC lacks the features of a typical autoimmune disease and responds poorly, if at all, to typical immunosuppressive therapies[3]. No effective medical therapy for halting disease progression has been identified, but ursodeoxycholic acid is being assessed. A median duration of 12 to 18 years from the time of diagnosis before patients develop end-stage liver disease has been observed. Among eligible patients, liver transplantation (LT) is currently the only life-extending therapy for patients with end-stage PSC, although the disease can recur in the allografted liver and be a cause of morbidity post-transplant[4].

CLINICAL FEATURES

Clinical manifestations

PSC affects primarily young and middle-aged men, especially patients with underlying inflammatory bowel disease. Approximately 70% to 80% of PSC patients in the United States have ulcerative colitis (UC)[5-10].

Conversely, approximately 2% to 7.5% of patients with UC[11] and 1.4% to 3.4% of patients with Crohn's disease[12] develop PSC. IBD can be diagnosed at any time during the course of PSC, and PSC can occur at any time during the course of IBD[13]. In general, however, IBD is diagnosed several years earlier than PSC[13]. PSC may also develop many years after proctocolectomy for colitis and IBD can develop many years after liver transplantation due to advanced PSC[11]. Whether PSC is a distinct entity in patients with and without IBD might be a clinically significant issue[14,15], but at present, there are not sufficient data to conclude that PSC occurring in patients without IBD is an entity separate from PSC found in association with IBD[11,16].

Asymptomatic patients represent about 15% to 40% of the patients at time of diagnosis in early studies[2]. More recently, more patients are identified at an earlier stage of the disease with fewer symptoms. One study showed that the majority of patients (greater than 55%) initially present with asymptomatically elevated liver enzymes[17]. Due to its close association to IBD, many cases come to medical attention when patients with IBD are screened for liver disease.

The clinical course of PSC is typically one of insidious worsening of cholestasis and eventual development of jaundice and end-stage liver disease[3]. As such, asymptomatic patients with PSC are at increased risk for developing symptoms over time. Fatigue and pruritus are reported as the most common symptoms. Jaundice, pain, fever and weight loss, cholangiocarcinoma, or manifestations of portal hypertension in advanced stages of liver disease are uncommon initial manifestations. In one recent study, the most common presenting symptoms were described as abdominal pain (20%), pruritus (10%), diarrhea (8%), jaundice (6%), fatigue (6%) and fever (4%)[17]. Another recent study from Sweden suggested that more patients without IBD are identified and the patients are older at diagnosis[18]. Symptoms of bacterial cholangitis usually are not manifested until patients undergo endoscopic intervention or surgical exploration of the biliary tract[19]. Cholangiocarcinoma develops in up to 23% of patients[20] and can occur relatively early and before onset of cirrhosis[3].

Impairments in health-related quality of life among individuals with PSC compared to the general population were confirmed in two independent populations[21,22]. Patients with cirrhosis form primary hepatocellular disease, however, reported lower health-related quality of life scores compared to patients with cholestatic liver disease[21].

Biochemical features
A cholestatic picture of liver function with elevations in serum alkaline phosphatase values are the biochemical hallmark of PSC. Increases between 3 and 10 times the upper limit of normal occur in 95% of cases. Serum alanine and aspartate aminotransferase levels are usually 2-3 fold higher than normal levels. The serum total bilirubin level is normal in 60% of individuals at diagnosis[2]. The liver function tests, however, may
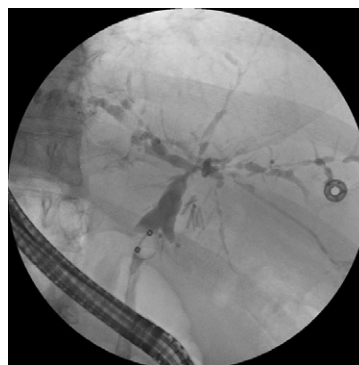

Figure 1 Cholangiographic finding in PSC. Cholangiogram demonstrating multifocal strictures with intervening saccular dilatation of both intrahepatic and extrahepatic bile duct characteristic of PSC. (Photograph courtesy of Dr. Rahul Pannala).

be normal and can fluctuate during the course of the disease[23].

Several prognostic models for PSC have been developed, most of which include age, serum bilirubin and histologic staging[5,7,9,10,24]. Most recently, a Mayo model for predicting the survival has been refined[25]. This uses the age of the patient, total serum bilirubin, aspartate aminotransferase levels, presence or absence of variceal bleeding and serum albumin as independent variables, and can be used in early stages of PSC, before onset of cirrhosis. The limitations of prognostic models include the inability to account for the development of cholangiocarcinoma and health-related quality of life[19]. Once decompensated cirrhosis is present, the Model for End-Stage Liver Disease (MELD) score[26] more accurately predicts survival and is more appropriately used in prioritizing patients for liver transplantation[3].

Serologic features
Currently, testing for specific autoimmune antibodies does not contribute to the diagnosis of PSC. The prevalent autoantibody reactivity is a perinuclear antineutrophilic autoantibody (pANCA), present in approximately 80% of patients but lacking in diagnostic specificity[27-30]. The unidentified antigenic reactant is not the proteinase (myeloperoxidase) of conventional pANCA. Other autoantibodies such as antinuclear antibodies and smooth muscle antibodies occur in 20% to 60% of patients, usually in lower titers than those observed in autoimmune hepatitis[31]; their fine antigenic specificity has not been established. Antimitochondrial antibodies are rarely found in patients with PSC[6], in keeping with the lack of overlap between PSC and primary biliary cirrhosis (PBC). The serological markers of autoimmune liver diseases are covered in more detail in other articles in this series.

Radiographic features
Cholangiography is considered to be the gold standard for the diagnosis of PSC[6]. In experienced hands, endoscopic retrograde cholangiopancreatography (ERCP) is successful in demonstrating the intra- and extra-hepatic biliary tree in 95% of the cases[3]. Segmental fibrosis of intrahepatic and/or extrahepatic bile ducts with saccular dilatation of normal intervening areas results in the characteristic beads-on-a-string appearance (Figure 1). Intrahepatic duct involvement is nearly universal with most patients affected
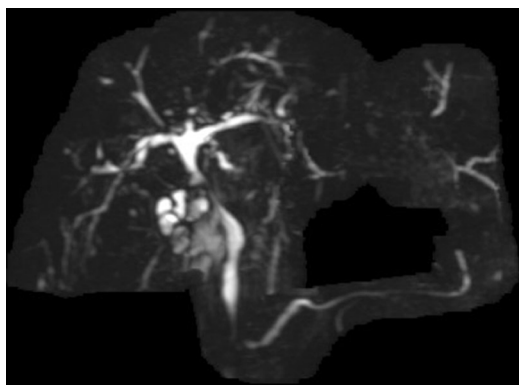
Figure 2 Cholangiographic findings in PSC. Magnetic resonance cholangiography demonstrating findings of PSC.

Figure 3 Fibro-obliterative lesions in PSC. Image shows an expanded portal area without two distinct fibro-obliterative lesions (arrows) in end-stage primary sclerosing cholangitis. There is no intact bile duct present in this portal area, only cross-sections of portal vein and hepatic artery branches (H&E, original magnification, 100 ×). Inset: Higher magnification of the fibro-obliterative lesion (Masson trichrome, × 400). (Photograph courtesy of Dr. Schuyler Sanderson).

by intrahepatic and extrahepatic disease[19]. Procedure-related complications from ERCP can occur in 3% to 8% of patients and include abdominal pain, pancreatitis, bleeding, common bile duct perforation, biliary sepsis and death[32-34].

The use of magnetic resonance cholangiography (MRC) for detecting PSC has been evaluated as a rapid, noninvasive examination of the biliary tract (Figure 2). MRC has no significant morbidity when performed in appropriately selected individuals, and avoids the potential adverse effects of radiation exposure and contrast media associated with ERCP[35]. For the detection of PSC, MRC has been found to be accurate and comparable to ERCP[36-39]. Moreover, one study has suggested it also results in cost savings when used as the initial test strategy for diagnosing PSC[34]. Factors that lead to difficulties in interpreting the MRC compared to ERCP include the presence of cirrhosis and PSC limited to the peripheral intrahepatic bile ducts[36]. The major disadvantage of MRC is that it is a purely diagnostic examination, although it can be used to identify patients who would benefit from subsequent therapeutic ERCP[19]. Although biliary tree changes on MRC aid in the diagnosis of PSC, they do not correlate with survival, as predicted by the Mayo Risk Score[38].

Histologic features

PSC is histologically characterized by damage, atrophy, and, ultimately, loss of medium- and large-sized bile ducts, within or outside the liver[40,41]. These are not typically captured in a percutaneous liver biopsy. The histological picture is complicated by the fact that separation of the disease process itself from the effects of distal obstruction of bile ducts can be challenging[41]. The smaller ducts are affected by the resultant obstruction and gradually disappear (ductopenia). The characteristic pathologic features of PSC are concentric periductal fibrosis ("onion-skinning") that progresses to a narrowing and then obliteration of the small bile ducts leaving a bile duct scar (Figure 3), but this is found in less than 15% of the patients with PSC[42]. Many of the biopsy changes, such as bile stasis, pseudoxanthomatous changes, Mallory bodies and copper accumulation, lack specificity for diagnostic
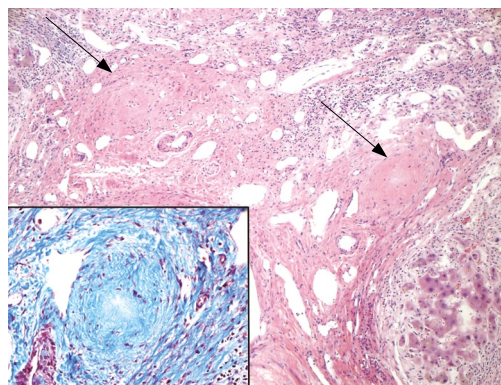
purposes[41], and can occur with chronic extra-hepatic bile duct obstruction from any cause[43]. Several stages can be recognized histologically, ranging from stages I to IV: cholangitis and portal hepatitis (stage I); periportal fibrosis or periportal hepatitis (stage II); septal fibrosis, bridging necrosis or both (stage III); and biliary cirrhosis (stage IV)[44]. Sampling error is a significant limitation of liver biopsy[41].

Liver biopsy in patients with radiographic evidence of PSC is not needed for diagnosis, although it may help in excluding other diseases[45]. Histological staging may be complementary to ERCP evaluation, but most times is not necessary. Liver biopsy should probably be limited to patients with a challenging presentation or those being investigated for small duct PSC or possible overlap syndrome with autoimmune hepatitis[17]. The presence of biliary dysplasia on liver histology has been proposed as a marker for eventual cholangiocarcinoma in PSC[46,47], but its use in clinical practice is limited by poor reproducibility of findings on pathologic interpretation[47].

VARIANT FORMS OF PSC

Small duct PSC

Small duct PSC refers to disease that affects bile ducts that are too small to be identified by ERCP. This entity is characterized by a consistent liver histology and radiographically normal bile ducts[48,49]. The proportion of small duct PSC to "large duct PSC" has been described as approximately 5%-15%[50,51]. Small duct PSC is believed to be a distinct entity from the large duct form, with a less aggressive course and less likely to lead to cholangiocarcinoma[50,52].

Overlap with autoimmune hepatitis

PSC with overlap features of autoimmune hepatitis has been reported both in the pediatric and adult populations of patients with PSC. In adults, the therapeutic response to immunosuppressants, in particular the autoimmune

hepatitis- or hepatocellular component of the overlap syndrome, can be excellent, and can lead to complete remission of disease activity[53]. The response to therapy might be dependent on the predominance of AIH or PSC features. The overlap syndromes of autoimmune liver diseases, including overlap of AIH and PSC in childhood are covered in more detail in other articles in this series.

IgG4-related sclerosing cholangitis
During the past decade, patients with steroid responsive sclerosing cholangitis have been described, often but not always associated with autoimmune pancreatitis[54]. Histological findings of lymphoplasmacytic infiltration and infiltration of IgG4-bearing plasma cells, and high serum IgG4 levels have been consistently observed and frequently required for diagnosis of autoimmune pancreatitis[55,56], and have also been observed in the hepatobiliary system. Described hepatobiliary changes have included stenosis of the bile ducts, biliary duct wall thickening, stenosis of the portal vein, portal fibrosis[57], and hepatic inflammatory pseudotumor[58]. Hepatobiliary involvement without pancreatic involvement suggests that IgG4-related sclerosing cholangitis could be a distinct entity from autoimmune pancreatitis[58]. IgG4-related sclerosing cholangitis is similar to PSC with regard to cholangiographic features, but, in contrast to PSC, is susceptible to steroid therapy and is reversible[58]. Therefore, identifying patients with IgG4-related sclerosing cholangitis and distinguishing them from patients with PSC could have major therapeutic implications[59]. Although very limited data exists on the prognosis and natural history of IgG4-related sclerosing cholangitis, it seems that the prognosis of these patients is more favorable than that of patients with PSC[54].

DISEASE-MODIFYING TREATMENTS
Different forms of medical treatment have been tried, but until now, no treatment has been proven efficient in randomized controlled studies.

Ineffective or unproven therapies
Several drugs, such as penicillamine[60], methotrexate[61], budesonide[62], colchicine[63], cladribine[64], cyclosporine[65], mycophenolate mofetil[66,67], etanercept[68], oral and transdermal nicotine[69,70], silymarin[71], pirfenidone[72], and pentoxifylline[73], have been evaluated in the treatment of this condition, but none of them has demonstrated convincing evidence of benefit and some are associated with significant side effects[62,66].

Tacrolimus was shown in a pilot study to cause significant improvement in serum liver biochemistries including alkaline phosphatase[74]. A subsequent study from Mayo Clinic supports previous observations that oral tacrolimus is associated with significant reductions in alkaline phosphatase levels in PSC[75]. However, in this study, the drug was not well tolerated, and the clinical benefit with oral tacrolimus with respect to disease activity in PSC appears to be limited.

Biologic therapy has been a major advancement in the current therapy of inflammatory bowel disease. There are no controlled trials evaluating the role of biologic therapy (e.g. infliximab and adalimumab) in the management of PSC.

Ursodeoxycholic acid
Multiple controlled studies have suggested that ursodeoxycholic acid (UDCA) has beneficial effects on liver biochemistries of patients with PSC[76-85]. A few studies have documented an improvement in liver histological appearance[76,79,82]. Other studies have not included liver histology as an outcome mainly because of sampling issues[85]. However, UDCA has not yet proven to prolong survival or improve outcome of PSC. All the trials performed to date have been limited by small number of patients and relatively short follow-up periods.

In an open label study performed at Mayo Clinic, 30 patients with PSC received high-dose (25-30 mg/kg per day) UDCA[83], and substantial reduction not only in serum hepatic biochemistries but also Mayo risk score were observed after 12 mo of therapy. Differences in expected 4-year survival based on Mayo Risk Score were substantial between historical placebo and high-dose UDCA groups. A previous placebo-controlled study conducted at Mayo Clinic in which 51 patients received lower doses of UDCA (13-15 mg/kg per day)[77] had showed beneficial effects limited to serum hepatic biochemistries, but no difference in predicted survival. An independent, double-blind, placebo-controlled trial[82] of UDCA at 20 mg/kg per day involving 102 patients observed improvement in liver biochemistries, cholangiographic appearance and liver histology after 2 years of therapy, but failed to have any significant effect on survival. No significant UDCA related adverse events were reported from either study. On the other hand, a European study[85] with 219 patients who were randomized to receive either high-dose UDCA (17-23 mg/kg per day) or placebo for 5 years did not observe any significant decrease of serum alkaline phosphatase in the UDCA-treated patients. There was no significant benefit from UDCA on survival without liver transplantation or prevention of cholangiocarcinoma, but the study was too small to exclude a significant beneficial effect on survival. A large, multicenter National Institutes of Health sponsored randomized trial of high-dose UDCA is currently underway[86].

Combination therapy
Combination therapy is a relatively new avenue of clinical research in the treatment of chronic cholestatic diseases. Drugs in monotherapy are often limited by efficacy and dose-related toxicity; combination therapy may hold the potential for improved efficacy through additive or synergistic effects, with the potential minimization of drug toxicities[87]. A controlled but nonrandomized study with 12 patients treated with a combination of low-dose prednisolone and colchicine failed to find any benefit in PSC[88]. The combination of UDCA and methotrexate was studied in 19 patients with

PSC and no changes in biochemistries from baseline values were seen compared to patients receiving UDCA alone[89]. An 8-wk pilot study evaluating the combination of prednisone or budesonide combined with UDCA failed to demonstrate significant beneficial effects to justify its use in patients with PSC[90]. In a small study with 15 patients, positive results were obtained with the combination of UDCA, prednisolone and azathioprine in decreasing liver biochemistry values[91], but evidence supporting long-term use of this therapy is lacking. Most recently, a study with 80 PSC patients randomized to either UDCA alone or the combination of metronidazole and UDCA showed that combination therapy led to improved serum alkaline phosphatase and Mayo Risk Score, but no significant effect on disease progression compared to UDCA alone[92].

Innovative approaches to medical therapy

Trials of antibiotics such as metronidazole and minocycline have been promising but inconclusive. A small study of docosahexaenoic acid (DHA) which improves CFTR function[93] is currently underway. Most promising for the near future are inhibitors of TNF action, antifibrotic agents (such as angiotensin-converting enzyme [ACE] inhibitors, sirolimus/rapamycin), and inhibitors of formation of toxic bile (such as 24-norursodeoxycholic acid)[94].

Endoscopic therapy

Some patients present with clinical and biochemical deterioration and exhibit a dominant stricture that involves the larger extrahepatic biliary ducts. Such lesions may be amenable to endoscopic or radiologic dilatation with or without a biliary drainage procedure, such as sphincterotomy and stenting[45]. This leads to improvement of clinical symptoms, liver biochemistries and cholangiographic findings. However, the endoscopic treatment of PSC has generated controversy, not only with regard to optimal management, but also its overall influence on survival. The use of endobiliary stents has been compared to balloon dilatation alone in patients with PSC[95,96], and a greater frequency of intervention-related complications including acute cholangitis was observed in patients with endobiliary stent placement. Repeated balloon dilatations of dominant biliary strictures resulted in improved actual survival rates compared to survival rates predicted by Mayo risk score[97,98].

Biliary surgery

Dominant strictures can also be managed surgically by dilatation or choledochojejunostomy, but this treatment has become uncommon with more recent advancement of endoscopic techniques and growing success of liver transplantation. At present, biliary surgery in patients with PSC, other than simple cholecystectomy, should be minimized and reserved for the selected rare noncirrhotic patients who have marked cholestasis or recurrent cholangitis caused by a dominant extrahepatic or hilar stricture not amenable to endoscopic or percutaneous dilatation[45]. In patients who may undergo liver transplantation, prior biliary surgery has been associated with a significantly longer operation time, greater intraoperative blood loss, and a higher incidence of biliary complications post-liver transplantation compared with those patients with no history of biliary surgery[99-103].

Liver transplantation

Although PSC is an uncommon disease, advanced-stage PSC remains among the most common indications for LT in the United States and in Europe[20]. Unique circumstances that require evaluation for possible LT include recurrent bacterial cholangitis despite intensive medical and endoscopic therapy, severe extrahepatic biliary obstruction that precludes operative repair, and uncontrolled peristomal variceal bleeding. Intractable pruritus may also be an indication for liver transplantation. Liver transplantation should be considered before the disease is too advanced, in order to enhance the long-term survival rates post-liver transplantation[104]. Prognostic models can aid in the timing of liver transplantation. Reports from single centers performing LT in PSC patients have demonstrated excellent survival rates of 90%-97% at one year, and 83%-88% at 5 years[105,106]. However, retransplantation rates seem to be higher for patients with PSC than other diagnoses[3].

Recurrence of PSC in the liver graft has been documented. Diagnosis of recurrence can be challenging, as non-specific bile duct injuries and strictures caused by allograft reperfusion injury, ischemia, rejection and recurrent biliary sepsis can mimic the findings of PSC post-transplantation and need to be carefully excluded before the diagnosis of recurrence can be established[107,108]. The frequency of recurrent PSC after liver transplantation remains controversial. The frequency of recurrent disease is estimated between 10% to 20% of patients[109], but a recent systematic review has indicated that publication bias might be a concern regarding this topic[4]. PSC might recur earlier at a higher ratio after living donor liver transplantation, particularly when the liver graft is obtained from a biologically related living donor[110]. Proposed risk factors for recurrent PSC include inflammatory bowel disease, prolonged cold ischemia time, number of cellular rejection episodes, previous biliary surgery, cytomegalovirus infection, and lymphocytotoxic cross-match[4] but these require further investigation. As more liver transplant recipients survive longer, the recurrence of disease may become the primary cause of morbidity and mortality in PSC[4].

Liver transplantation in autoimmune liver diseases is covered in more detail in another article in this series.

DISEASE-RELATED COMPLICATIONS

Fatigue and pruritus

Pruritus is a prevalent problem in patients with chronic cholestatic disease[111]. Cholestyramine is effective in 80% to 90% of the patients, and represents the first-line of treatment[112]. Other drugs that have been commonly used for the treatment of pruritus include rifampin[113],

opioid antagonists[114,115] and ondansetron[116]. Sertraline has been demonstrated to have positive effects on pruritus in cholestatic liver disease in a small study[117]. Etanercept has also had positive effects on pruritus in patients with PSC in a small study not originally designed to primarily assess the effect of that drug on pruritus[68]. In controlled trials, UDCA has not been associated with improvement in pruritus, but those studies were not specifically designed for that purpose. Intractable pruritus may be an indication for LT[19].

Fatigue is also noted to be a prevalent problem in patients with chronic cholestatic disease, and a major determinant of impaired health related quality of life[118]. However, no medical therapy is available for treatment.

Metabolic bone disease

Severe bone disease in PSC patients is more common than expected, but less frequent than that reported in primary biliary cirrhosis[119]. Patients with longer duration of IBD, and more advanced liver disease were found to be at higher risk of severe osteoporosis[119]. In this same study, Angulo *et al*[119] found that the severity of osteopenic disease in PSC seems to increase as liver disease advances, but this finding was not confirmed in a subsequent study by Campbell *et al*[120]. Bone mineral densitometry measurements are the only test helpful in evaluating progression of osteopenia in patients with PSC, and the presence, severity and progression of the bone disease cannot be accurately evaluated by routine clinical, biochemical, or histological variables[119]. This is important since most patients with PSC and advanced liver disease undergo liver transplantation. Early post-transplant bone loss remains a clinically significant problem and frequently leads to fracturing in a third of patients with PSC when the pre-transplant bone mineral density is below the fracture threshold[119,121].

For treatment of osteoporosis and osteopenia, calcium and vitamin D supplementation are recommended, and in selected cases, bisphosphonates may be indicated. Many new drugs have become available for the treatment of post-menopausal osteoporosis, and more studies are needed to determine the role of these treatments in primary sclerosing cholangitis.

Gallbladder stones and polyps

Cholelithiasis has been noted in 26% of individuals with PSC, with the majority being asymptomatic[122]. Consideration should be given to performing a cholecystectomy if cross-sectional imaging results in the identification of gallbladder polyps given the potential for neoplastic transformation in PSC[123].

Peristomal varices

A special complication of portal hypertension in PSC patients with an ileal stoma is the development of peristomal varices[45]. Those develop within the adhesions between the ileal (portal) veins and the anterior abdominal wall (systemic) veins. Patients bleeding from peristomal varices often present with recurrent hemorrhagic episodes. Bleeding from the peristomal varices is more difficult to treat than bleeding from esophageal varices. Local treatment to control and prevent bleeding is usually unsuccessful in the long term. Liver transplantation should be considered for treatment. If that is not possible, peristomal variceal bleeding can be controlled with a portosystemic shunt[2].

Dominant stricture

A dominant stricture, defined by Stiehl *et al*[124] as a diameter in the common duct of less than 1.5 mm and in the hepatic duct of less than 1 mm, is a frequent finding and occurs in 45% to 58% of patients during follow-up. Stenotic lesions in PSC are thus far more often benign than malignant in nature[124]. Endoscopic treatment of dominant stenoses improves cholestasis and prolongs survival in comparison to predicted survival[97,125]. Prophylactic antibiotic administration prior to endoscopic manipulation of the biliary tree is recommended by the American Society for Gastrointestinal Endoscopy in the setting of bile duct obstruction to prevent contamination during the cannulation of the bile duct[126].

Bacterial cholangitis

Bacteriobilia is found in the majority of PSC patients[127], but, as previously mentioned, bacterial cholangitis usually is not manifested until patients undergo endoscopic intervention or surgical exploration of the biliary tract. Bacterial cholangitis is common in patients with dominant stricture and requires antibiotic treatment[45]. It may also occur after endoscopic procedures or in patients with bile duct stones or tight strictures[128], warranting prophylactic antibiotic administration prior to endoscopic manipulation of the biliary tree. Most biliary infections in patients with obstructive disease of the biliary tract are caused by aerobic enteric organisms such as *Escheria coli*, *Klebsiella* species, and *E. faecalis*[129]. Recurrent episodes of bacterial cholangitis can be an indication for liver transplantation in patients with otherwise preserved liver function. Prophylaxis with antibiotics has not been proven to be of benefit[128], but patients with recurrent cholangitis should be advised to seek medical attention rapidly and start antibiotics at the first sign of biliary infection.

Malignancy

Cholangiocarcinoma: Primary sclerosing cholangitis carries an increased risk of hepatobiliary malignancy, especially cholangiocarcinoma (CCA)[8,130]. The development of CCA is the most lethal complication of PSC. Cholangiocarcinoma can arise at any stage of PSC, although, in general, the incidence is higher in more advanced disease[5,131]. There are no clinical features that predict the diagnosis of CCA, and diagnosis can be challenging.

The cumulative life-time incidence of CCA is estimated as 6% to 23%[20]. The reported prevalence of CCA in explanted livers and autopsy is much higher, approximately 30% to 42%[9,132]. Overall, up to 50%

of CCA cases are detected synchronous with the PSC diagnosis or within one year of diagnosis of PSC[130,133-136]. Based upon the same reported series, the incidence of CCA during follow-up, starting at 1 year after the diagnosis of PSC, can be calculated as being between 0.5% and 1.5% per year. The malignancy usually develops in the fourth decade of life, whereas CCA in patients without PSC usually develops much later in life, in their seventh decade of life[20].

Risk factors for the development of CCA in PSC have not been clearly identified, but older age, longer duration of IBD and smoking behavior have been associated with an increased risk for development of CCA in patients with PSC. Finding biliary dysplasia on liver histology has also been proposed as a precursor in the development of cholangiocarcinoma[46,47].

The diagnosis of CCA can be challenging. The role of serum CA19-9 level in the diagnosis of CCA is controversial. There are no tumor markers which are specific for cholangiocarcinoma. In the context of PSC, a serum CA19-9 level greater than 100 U/mL has been reported to have a sensitivity of 75% and a specificity of 80% for presence of cholangiocarcinoma[137,138]. A recent study from the Mayo Clinic found that a serum level greater than 129 U/mL provided a sensitivity of 78.6% and specificity of 98.5% for CCA in PSC[139]. Even though these studies suggest CA 19-9 is an accurate test to diagnose cholangiocarcinoma, CA 19-9 was only found to identify patients with advanced, unresectable CCA, and thus its use is not appropriate as a screening test[139]. Ultrasonography, computed tomography, and magnetic resonance have inadequate sensitivity to distinguish CCA from PSC. Endoscopic biopsy and biliary brushing for cytology, digital image analysis, and fluorescent *in situ* hybridization are noted for good specificity but poor sensitivity in detecting CCA[19].

Patients with PSC and CCA have a very poor outcome, with median survival of approximately 5 to 11 mo[20,135,140]. Even though survival of patients in whom CCA was found incidentally by histological examination of the explanted liver has been reported to be good[5], in general, LT for patients with CCA results in a low success rate[141-144]. However, more recent data from investigational protocols have suggested better outcomes in highly selected individuals. The use of pretreatment radiotherapy and subsequent capecitabine for 2 to 3 wk prior to LT at Mayo Clinic has yielded a 3- and 5-year actuarial survival of 82%[145]. The use of brachytherapy and continuous 5-fluoracil infusion before liver transplantation in Nebraska resulted in 45% long-term cancer-free survival after follow-up for a median of 7.5 years[146]. Curative resection among individuals with early-stage cholangiocarcinoma may also be of benefit in PSC[133], although recent data suggest that transplant with neoadjuvant chemoradiation with localized, node-negative hilar CCA may achieve better survival with less recurrence than conventional resection[145,147].

Recent studies have suggested that the incidence of CCA in patients with PSC treated with UDCA is lower than expected and decreases with time of therapy[141,148]. Further studies are needed to confirm this finding.

Colonic dysplasia and carcinoma: Whether the presence of PSC increases the risk of colonic dysplasia and carcinoma in ulcerative colitis is controversial[149,150]. Patients with PSC and UC have been found to have an increased incidence of colonic carcinomas compared to patients with ulcerative colitis alone in a few studies[136,151-153], however, contradictory results have also been presented[154,155]. The size, design, end-points, and populations involved in these studies have varied, and critical review suggests that colorectal cancer is more common in the setting of PSC[150]. Furthermore, PSC patients with UC remain at an increased risk for developing colorectal dysplasia and carcinoma after they have undergone liver transplantation[11,156]. The immunosuppressive treatment after liver transplantation may have an impact on the development of cancer.

Two studies have indicated that UDCA reduced the incidence of colonic dysplasias and/or carcinomas[157,158].

Gallbladder neoplasia: Dysplasia, adenomas and carcinoma of the gallbladder have been described in PSC but are less common than cholangiocarcinoma. PSC is recognized as one of the major risk factors for both gallbladder and bile duct carcinoma[159]. A recent study reported statistically significant association between hilar/intrahepatic biliary neoplasia and gallbladder neoplasia, suggesting a "field effect" in the intrahepatic and extrahepatic biliary tree in PSC[160]. Identification of gallbladder polyps on cross-sectional imaging should lead to consideration for cholecystectomy[123]. Large studies on this subject have not been performed.

Hepatocellular carcinoma: Although patients with cirrhotic stage PSC may also be at risk for developing hepatocellular carcinoma, this malignancy occurs infrequently[131,136,161].

PREGNANCY AND PSC

Little is known regarding the natural history and potential complications of pregnancy in patients with PSC. There are very few case reports[162,163] and one small series of thirteen pregnancies in 10 patients with PSC[164] that describe the fetal and maternal outcome of pregnancy in PSC. Although previously described, it appears that hepatic disease activity is not significantly worsened during the gestational period[2]. Nonetheless, patients with PSC who become pregnant require close monitoring[162]. Regular blood tests, including serum bilirubin and aminotransferase levels, are essential. In the event that the patient develops symptoms worrisome for obstruction, an ultrasound is a safe diagnostic test and may detect the presence of dominant strictures or stones; it lacks sensitivity however. MRC might have an emerging role in pregnancy, and more invasive tests such as ERCP might be required.

CONCLUSION

Primary sclerosing cholangitis is a presumed immune-mediated liver disease of young men associated with significant morbidity and mortality. However, there is no proven medical treatment available for it. Further studies are needed for better understanding of the pathophysiology of the disease and for development of an optimal therapeutic strategy for patients with PSC to improve health related quality of life and halt progression of disease, thereby decreasing incidence of complications of advanced liver disease, and the need for transplantation.

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